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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/531,095	04/07/2005	Henry M Krause	1889-00900	5757

23505 7590 11/13/2007

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EXAMINER	
.SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
11/13/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/531,095	KRAUSE ET AL.	
	Examiner	Art Unit	
	Dana Shin	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-13,15-17 and 20-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-13,15-17 and 20-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 31, 2007 has been entered.

Status of Claims

Currently, claims 10-13, 15-17, and 20-23 are pending and under examination on the merits.

Response to Arguments

Applicant's arguments with respect to claims 10-13, 15-17, and 20-23 have been considered but are moot in view of the new ground(s) of rejection. See below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 10 and claims 11-13, 15-17, 20-23 (by virtue of claim dependency) are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims comprise an RNA fusion molecule having at least one insulator sequence comprising "stretches of identical nucleotides" flanked by identical restriction sites. With regard to the term "insulator sequence" and the claim language "stretches of identical nucleotides", the specification states, "Examples of suitable insulator elements include, but are not limited to stretches of 4-5 identical nucleotides (eg, adenosines) coupled with paired restriction sites that do not interact with the tag or bait sequences." on page 15. The specification also teaches that the "stretches of identical nucleotides" can consist of 8-10 adenosine nucleotides. See page 18. As broadly and openly described, "stretches of identical nucleotides" recited in the claims are not limited to 4-5 or 8-10 identical adenosine nucleotides, but are open to an infinite number of identical nucleotides. Therefore, one of ordinary skill in the art cannot ascertain the metes and bounds set forth by the language "stretches of identical nucleotides" in the claims, thereby rendering the claims indefinite.

Claims 10-13, 15-17, and 20-23 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. Since there is no recitation of specific orientation or spatial relationship among the different elements constituting the claimed RNA fusion molecule (i.e., the location of RNA tags in relation to target RNA sequence/insulator sequence), one of ordinary skill in the art cannot

ascertain the complete structure of the claimed invention as a whole, thereby rendering the claims indefinite.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 10, 12, 15-17, and 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Srisawat et al. (citation of record) in view of Skerra et al. (*Biomolecular Engineering,* 1999, 16:79-86), Miki et al. (US 5,595,895), and Colgin et al. (*Protein Science,* 1998, 7:667-672).

The claims are drawn to an RNA fusion molecule comprising a target RNA sequence, at least one insulator sequence comprising stretches of identical nucleotides flanked by identical restriction sites, at least two different RNA tags, wherein at least one RNA tag interacts with a ligand in a reversible fashion, wherein the RNA tags are S1, Streptotag, or D8, and a vector comprising the RNA fusion molecule.

The specification teaches that the claimed insulator sequence is functionally equivalent to and synonymous in meaning with a spacer. See page 15.

Srisawat et al. teach a fusion RNA molecule comprising two different RNA tags, S1 and D8. They teach that the RNA tags can be used to rapidly and specifically isolate a particular precursor or product form of RNA of interest from RNPs or characterization of RNPs containing lethal mutations (page 161). They expressly teach that one of main considerations in constructing affinity tag molecules is the folding problem. They explicitly teach that the "folding problem is "simply" a matter of inserting the tag in such a way that both the tag and the RNA of interest remain correctly folded." (page 158) They teach that one potential solution to the steric blockage problem is to "place a short spacer between the tag and the main body of the RNA". See page 159. They teach that several factors need to be taken into consideration in designing the RNA tag fusion molecule: availability of the potential affinity resins, ability to elute bound RNA without co-eluting nonspecific contaminants, and ability to have a high affinity only for specific RNAs and RNPs (page 157). Srisawat et al. do not teach that the spacer (or insulator) sequence comprise identical nucleotides flanked by identical restriction sites, nor do they teach that the RNA tag interacts with a ligand in a reversible fashion.

Skerra et al. teach that the Strep-tag binds specifically to streptavidin in a reversible fashion, and therefore, the Strep-tag can be applied for efficient purification of corresponding fusion proteins on affinity columns with immobilized streptavidin. They teach that the Strep-tag can be inserted within a fusion protein; however, it must be ensured that the Strep-tag is "sterically accessible between the two protein domains". See page 85. They teach, "The Strep-tag (II) may therefore provide an ideal device for the rapid functional screening of purified gene products in modern proteome research." See page 86.

Miki et al. teach a DNA cloning system wherein the exogenous nucleotide sequence insert is flanked by identical SfiI restriction sites, wherein the SfiI recognizes "GGCCNNNNNGGCC", wherein the "N" nucleotide can be any one of the four nucleotides. They teach that the flanking SfiI restriction sites allow nucleotide sequence inserts to be excised as a single fragment by using only a single restriction enzyme. See column 11.

Colgin et al. teach that the "AAAAA" nucleotide sequence functions as a spacer by providing a space of 10.7 angstroms. See pages 671-672.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the RNA fusion molecule of Srisawat et al. by incorporating the reversible Strep-tag of Skerra et al., and the SfiI restriction sites ("GGCCNNNNNGGCC") of Miki et al., wherein the SfiI restriction sites comprise the "AAAAA" spacer sequence of Colgin et al. in place of the "NNNNN" of the SfiI sequence.

One of ordinary skill in the art would have been motivated to make such modifications into the RNA fusion molecule of Srisawat et al. because Srisawat et al. expressly taught that adding a "short spacer" into the fusion molecule would help prevent folding problems caused by

steric blockage, and because Colgin et al. taught that the penta-sequence of "AAAAA" can function as a spacer because it provides a space of 10.7 angstroms. Further, the ordinary skilled artisan would have been motivated to utilize the SfiI restriction endonuclease sequence of Colgin et al. to flank the tag sequences, because the SfiI restriction endonuclease sequence provides flexibility in choosing the "NNNNN" sequence and because one can easily and cheaply clone or shuffle a desired tag by using only a single restriction endonuclease, instead of two different endonucleases. As such, flanking the RNA tag inserts between the two identical SfiI restriction endonuclease sequences of "GGCCAAAAAGGCC" is not only cost-effective but also convenient because such sequence serves two purposes simultaneously. Further, the skilled artisan would have been motivated to replace the S1 or D8 tag of Srisawat et al. with the Strep-tag of Skerra et al., because Skerra et al. taught that the Strep-tag binds its ligand in a reversible fashion and that the Strep-tag is an ideal device for the rapid functional screening of purified gene products in modern proteome research. Since all the components, elements, skills, and knowledge required to arrive at the claimed invention were within the technical grasp of one of ordinary skill in the art at the time of the invention, one of ordinary skill in the art would have had a reasonable expectation of success in making the claimed invention, and therefore, the instantly claimed invention taken as a whole would have been *prima facie* obvious at the time of the filing.

Claims 10-13, 15-17, and 20-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Srisawat et al., Skerra et al., Miki et al., and Colgin et al. as applied to claims

10, 12, 15-17, and 20-22 above, further in view of Johansson et al. (citation of record), and Bardwell et al. (citation of record).

Claims 10, 12, 15-17, and 20-22 are described above.

Claims 11, 13, and 23 are drawn to an RNA fusion molecule comprising two identical RNA tags, or comprising one S1 and one MS2.

The combined references of Srisawat et al., Skerra et al., Miki et al., and Colgin et al. teach an RNA fusion molecule comprising two non-identical RNA tags, further comprising an insulator sequence flanked by identical restriction sites, wherein the fusion molecule comprises a Strep-tag that interacts with its ligand in a reversible fashion. The combination of the cited prior art does not teach that the RNA tags are identical or the fusion molecule comprises S1 and MS2 as RNA tags.

Johansson et al. teach that MS2 coat protein specifically binds to RNA hairpins and this protein-RNA interaction has been extensively studied as a model for the rapidly expanding class of proteins that bind RNA hairpins.

Bardwell et al. teach affinity RNA tag purification method for RNA-protein complexes. They teach that an RNA containing two tandem RNA tags (two R17 recognition sites adjacent to each other) has stronger affinity to target coat protein matrix than that containing only one RNA tag (pages 6590-6591, 6593-6594; Figures 3-4).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make the presently claimed fusion RNA molecule comprising a target RNA sequence, at least one insulated sequence, and at least two RNA tags.

One of ordinary skill in the art would have been motivated to modify the structure of RNA fusion molecules of Srisawat et al. in view of the teachings of the combined prior art references, because Srisawat et al. expressly taught major factors to consider with regard to the specificity of RNA affinity tags (pages 157 and 159). One of ordinary skill in the art would have had a reasonable expectation of success in modifying the RNA fusion molecules of Srisawat et al. to arrive at the instantly claimed RNA fusion molecule because the use of MS2 in studying protein-RNA interaction was known in the art as taught by Johansson et al., and because placing two identical RNA tags in tandem orientation was known to be more efficient as evidenced by the teachings of Bardwell et al. Further, one of ordinary skill in the art would have arrived at the claimed invention with a reasonable expectation of success because Srisawat et al. expressly taught that it is necessary to generate and test several tagged RNA constructs to ensure their ability to bind to the affinity matrix. In other words, since the necessity to test various tagged RNA constructs was known in the art, one of ordinary skill in the art would have been sufficiently motivated to test a number of different tagged RNA constructs and would have succeeded in making a specific tagged RNA construct as claimed in the instant case through routine optimization experimentation. Accordingly, the claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
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Art Unit 1635

/J. E. Angell/
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